information called for in 37 CFR §1.121(b), while providing clarity to the Office on the specific changes introduced by the amendment.

REMARKS

Reconsideration of the rejections is respectfully requested.

The status of the claims is as follows:

Amended:	9, 16
Cancelled:	10
Pending:	1-9, 11-16

The claims have been amended to more clearly define the invention. Support for the amendments can be found, for example, at 4: 10-18; 7: 34-38; and 7: 57-65. No new matter is added by the amendments.

Claim Rejections – 35 U.S.C. §112, First Paragraph

Claims 9-16 stood rejected under 35 U.S.C. §112, first paragraph, based on an assertion that certain subject matter was not enabled. The rejection is framed based on the wording of the prior claims. Applicants respectfully submit the invention as now framed can be practiced with ordinary skill in the art of monoclonal antibodies.

The basis for the rejection appears to be an assertion that "monoclonal antibody binding specificity is art recognized to be highly variable," and thus undue experimentation would be required to practice the invention. As a first matter, since the Office appears to be relying on asserted facts within the personal knowledge of its agents, if the rejection is maintained Applicants will need an affidavit supporting such asserted facts, as required by MPEP §2144.03.

Applicants teach how to make and screen the hybridomas that create the claimed antibody. In Enzo Biochem, Inc. v. Calgene, Inc., 188 F.3d 1362, 1372-74 52 USPQ2d 1129, 1136-38 (Fed.Cir. 1999), the Federal Circuit approved a trial court determination in a comparable art that a person of ordinary skill would be a junior faculty member with one or two years of relevant experience or a postdoctoral student with several years of experience.

Applicants respectfully submit that this level of skill is an appropriate measure of skill in the present context.

Any assertion that Applicants' teachings and knowledge in the art is insufficient to allow a skilled artisan to make and use the invention is answered by In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed.Cir. 1988), which is exactly on point. In Wands, the claim at issue read:

> 1. An immunoassay method utilizing an antibody to assay for a substance comprising hepatitis B-surface antigen (HBsAg) determinants which comprises the steps of:
>
> contacting a test sample containing said substance comprising HBsAg determinants with said antibody; and
>
> determining the presence of said substance in said sample;
>
> wherein said antibody is a monoclonal high affinity IgM antibody having a binding affinity constant for said HBsAg determinants of at least 10^9 M^{-1}.

In overturning the enablement rejection asserted by the Office, the Court stated:

> The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody.

Wands, at 740. The routine effort by those of substantial skill to arrive at the antibodies of the invention is no more undue than in Wands.

In a more recent case, the Federal Circuit affirmed a finding on Summary Judgment that the following claim is enabled:

> A monoclonal antibody which specifically binds to an antigen on nonmalignant, immature human marrow cells, *wherein* said antigen is stage specific and not lineage dependent, and *said antigen is also specifically bound by the antibody produced by the hybridoma deposited under ATCC Accession No. HB-8483...*

Johns Hopkins University v. CellPro, Inc., 152 F.3d 1342, 1347, 47 USPQ2d 1705, 1719 (Fed.Cir. 1998) (emphasis as quoted by the court; the claim text which is not shown was omitted by the court and deemed by the court to be immaterial). The last quoted clause of the claim defines the antibody as recognizing the cell surface antigen CD34. The defendant asserted that the specification does not teach one to make antibodies that bind CD34, other than a disclosed particular "anti-My-10 antibody." The Court, in the voice of Judge Lourie, a jurist who has frequently ruled against expansive biotechnology claims, noted in discounting an affidavit on the difficulty of obtaining CD34 monoclonals:

> The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention.

Johns Hopkins, at 1360, *quoting*, PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed.Cir. 1996).

Applicants respectfully submit that, in light of the above discussion, it should be clear that the invention as claimed was enabled.

Rejections Under 35 U.S.C. §103(a)

The Office Action asserts that the claims would have been obvious in view of Makita, as represented by one or both of a 1992 J. Biol. Chem. article or a 1992 Science article, in further view of Harlow, which is text excerpted from a laboratory manual on antibody techniques, or in further view of another article on antibody techniques. Applicants respectfully traverse.

Makita is about polyclonal antibodies. The Office Action links this disclosure to monoclonal antibodies with the following argument:

> ... Harlow et al. teach that hybridomas produce monoclonal antibodies that have homogeneous specificity and affinity for antigen thereby providing an expectation of success [as to binding affinity]...

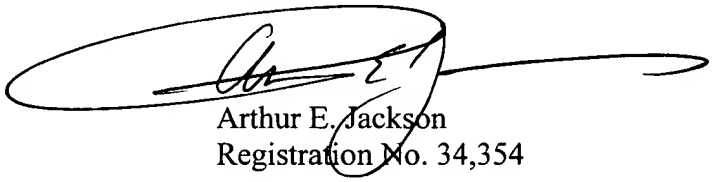
The above-quoted assertion is a textbook example of borrowing from the applicant's disclosures to make a hindsight reconstruction of the invention.

The above assertion, moreover, is disproved by reference to more germane art. Horiuchi, J. Biol. Chem. 266: 7329-7332, 1991 teaches a *monoclonal* antibody that recognizes AGE-ε-amino-caproic acid. However, as indicated in the attached Declaration of inventor Dr. Henry W. Founds in parent case 08/367,507 (now US Patent 5,744,318), this monoclonal antibody lacks the affinity recited in Applicants claims (and fall short by two orders of magnitude). It clearly was not obvious at the time of the invention that monoclonal antibodies with the recited affinity could be made. Accordingly, Applicants respectfully submit that the rejection must be withdrawn.

Conclusion

Applicants thank the Examiner for the Office Action and believe this response to be a full and complete response to such Office Action. Accordingly, favorable reexamination, reconsideration in view of this response and allowance of the pending claims are earnestly solicited. In light of the above discussion and amendments, Applicants respectfully submit that the claims are in condition for allowance. The issuance of a Notice of Allowance is earnestly solicited.[2]

Respectfully submitted,



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[2] **FEE DEFICIENCY**

IF ANY ADDITIONAL EXTENSION IS REQUIRED, PLEASE CONSIDER THIS PAPER A PETITION FOR SUCH AN EXTENSION; ANY FEE FOR THE EXTENSION REQUIRED FOR CONSIDERATION OF THIS PAPER BUT NOT ENUMERATED ABOVE OR IN A TRANSMITTAL OR OTHER ASSOCIATED PAPER CAN BE CHARGED TO ACCOUNT NO. 04-0480.

AND/OR

IF ANY ADDITIONAL FEE IS REQUIRED FOR CONSIDERATION OF THIS PAPER, PLEASE CHARGE ACCOUNT NO. 04-0480.

What is claimed is:

1. Monoclonal antibody 4G9 produced by hybridoma 4G9, deposited with the American Type Culture Collection (ATCC) and assigned Accession Number CRL 11626, or an antigen binding fragment thereof reactive with in vivo produced advanced glycosylation endproducts (AGEs).

2. The monoclonal antibody or antigen binding fragment thereof of claim 1, which specifically binds to serum-AGE proteins, serum-AGE lipids, serum-AGE peptides, LDL-AGE, Hb-AGE, or collagen-AGE.

3. A humanized or chimetic human-murine antibody of the monoclonal antibody of claim 1.

4. The antigen-binding fragment of the monoclonal antibody of claim 1, selected from the group consisting of a single chain Fv fragment, an F(ab') fragment, an F(ab) fragment, and an $F(ab')_2$ fragment.

5. The monoclonal antibody or fragment thereof of claim 1 which is a murine IgG isotype antibody.

6. A labeled antibody wherein the antibody is the antibody of claim 1.

7. A hybridoma deposited with the American Type Culture Collection (ATCC) and assigned Accession Number CRL 11626.

8. A pharmaceutical composition containing an anti-AGE antibody in combination with a pharmaceutically acceptable carrier; wherein said anti-AGE antibody is the monoclonal antibody in accordance with any of claims 1-3 or 4.

Sub B1 A1

9. A monoclonal antibody, or an antigen binding fragment thereof reactive with in vivo produced advanced glycosylation endproducts (AGEs), wherein [antigen binding by] the antibody or fragment is [competed by lysine or] selected such that antigen binding measured by binding competition by 6-aminocaproic acid browned with glucose [with an IC50 of 5 X 10-4 M or less, wherein the concentration of browned

lysine or 6-aminocaproic acid is with respect to the lysine or 6-aminocaproic acid subjected to the browning reaction.] matches that of a reference binding moiety which is monoclonal antibody 4G9 produced by hybridoma 4G9, deposited with the American Type Culture Collection (ATCC) and assigned Accession Number CRL 11626 or a fragment thereof corresponding to the antigen binding fragment.

[10. The monoclonal antibody of claim 9, wherein antigen binding by the antibody or fragment is competed by 6-aminocaproic acid browned with glucose with an IC50 of 5 X 10-4 M or less.]

11. The monoclonal antibody or antigen binding fragment thereof of claim 9, which specifically binds to serum-AGE proteins, serum-AGE lipids, serum-AGE peptides, LDL-AGE, Hb-AGE, or collagen-AGE.

12. A humanized or chimetic human-murine antibody of the monoclonal antibody of claim 9.

13. The antigen-binding fragment of the monoclonal antibody of claim 9, selected from the group consisting of a single chain Fv fragment, an F(ab') fragment, an F(ab) fragment, and an $F(ab')_2$ fragment.

14. The monoclonal antibody or fragment thereof of claim 9, which is a murine IgG isotype antibody.

15. A labeled antibody wherein the antibody is the antibody of claim 9.

16. A pharmaceutical composition containing an anti-AGE antibody in combination with a pharmaceutically acceptable carrier; wherein said anti-AGE antibody is the monoclonal antibody in accordance with any of claims 9, 11-12 or 13.

What is claimed is:

1. Monoclonal antibody 4G9 produced by hybridoma 4G9, deposited with the American Type Culture Collection (ATCC) and assigned Accession Number CRL 11626, or an antigen binding fragment thereof reactive with in vivo produced advanced glycosylation endproducts (AGEs).

2. The monoclonal antibody or antigen binding fragment thereof of claim 1, which specifically binds to serum-AGE proteins, serum-AGE lipids, serum-AGE peptides, LDL-AGE, Hb-AGE, or collagen-AGE.

3. A humanized or chimetic human-murine antibody of the monoclonal antibody of claim 1.

4. The antigen-binding fragment of the monoclonal antibody of claim 1, selected from the group consisting of a single chain Fv fragment, an F(ab') fragment, an F(ab) fragment, and an $F(ab')_2$ fragment.

5. The monoclonal antibody or fragment thereof of claim 1 which is a murine IgG isotype antibody.

6. A labeled antibody wherein the antibody is the antibody of claim 1.

7. A hybridoma deposited with the American Type Culture Collection (ATCC) and assigned Accession Number CRL 11626.

8. A pharmaceutical composition containing an anti-AGE antibody in combination with a pharmaceutically acceptable carrier; wherein said anti-AGE antibody is the monoclonal antibody in accordance with any of claims 1-3 or 4.

9. A monoclonal antibody, or an antigen binding fragment thereof reactive with in vivo produced advanced glycosylation endproducts (AGEs), wherein the antibody or fragment is selected such that antigen binding measured by binding competition by 6-aminocaproic acid browned with glucose matches that of a reference binding moiety which is monoclonal antibody 4G9 produced by hybridoma 4G9, deposited with the American Type Culture Collection

(ATCC) and assigned Accession Number CRL 11626 or a fragment thereof corresponding to the antigen binding fragment.

Please cancel claim 10 without prejudice or disclaimer.

11. The monoclonal antibody or antigen binding fragment thereof of claim 9, which specifically binds to serum-AGE proteins, serum-AGE lipids, serum-AGE peptides, LDL-AGE, Hb-AGE, or collagen-AGE.

12. A humanized or chimetic human-murine antibody of the monoclonal antibody of claim 9.

12. The antigen-binding fragment of the monoclonal antibody of claim 9, selected from the group consisting of a single chain Fv fragment, an F(ab') fragment, an F(ab) fragment, and an $F(ab')_2$ fragment.

14. The monoclonal antibody or fragment thereof of claim 9, which is a murine IgG isotype antibody.

15. A labeled antibody wherein the antibody is the antibody of claim 9.

16. A pharmaceutical composition containing an anti-AGE antibody in combination with a pharmaceutically acceptable carrier; wherein said anti-AGE antibody is the monoclonal antibody in accordance with any of claims 9, 11-12 or 13.